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1. Document ID: WO 9012885 A JP 2919961 B2 AU 9056591 A FI 9104924 A NO 9104119 A EP 548070 A1 JP 05504465 W AU 649613 B EP 548070 B1 DE 69031225 E CA 1340245 C

L2: Entry 1 of 1 File: DWPI Nov 1, 1990

DERWENT-ACC-NO: 1990-348488
DERWENT-WEEK: 199934

TITLE: New antibody prepn. - comprises antibody binding to antigens associated with squamous cell carcinoma, used for diagnosing and treating tumours

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

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Terms	Documents
Longenecker[in] and Diener[in]	1

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Previous Page Next Page

L27 ANSWER 1 OF 7 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 1990012885 PCTFULL ED 20020513
TITLE (ENGLISH): MONOCLONAL ANTIBODY FOR DIFFERENTIATION OF SQUAMOUS CELL CARCINOMA ANTIGENS AND METHOD OF USE FOR SAME
TITLE (FRENCH): ANTICORPS MONOCLONAL POUR LA DIFFERENCIATION D'ANTIGENES DE CARCINOMES DE CELLULES SQUAMEUSES ET PROCEDE D'UTILISATION
INVENTOR(S): SAMUEL, John;
LONGENECKER, B., Michael;
STANCZYK-BRZEZINSKA, Grazyna;
WILLANS, David;
HONORE, Louis, H.;
HAINES, Deborah, M.;
DIENER, Erwin;
DING, Lei
PATENT ASSIGNEE(S): SAMUEL, John;
LONGENECKER, B., Michael;
STANCZYK-BRZEZINSKA, Grazyna;
WILLANS, David;
HONORE, Louis, H.;
HAINES, Deborah, M.;
DIENER, Erwin;
DING, Lei
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9012885	A1	19901101

DESIGNATED STATES
W: AT AU BE CH DE DK ES FI FR GB IT JP LU NL NO SE US
APPLICATION INFO.: **WO 1990-US2152** **A 19900420**
PRIORITY INFO.: US 1989-341,402 19890421
AI **WO 1990-US2152** **A 19900420**

DETD . . . al.,
Cancer Res. 47: 5684 (1987) and European Patent Application (InTek Diagnostic) Number 87311402,0, (The latter reference summarizes the characteristics of many anti-SCC **antibodies**.) No
characterization of the antigen recognized by this **antibody** has
been reported. The antigen is presumed to be an intermediate type filament, based on electron microscope data. The European patent application states that the antigen is not a cytokeratin. The **antibody** is specific for basal layer of stratified **squamous** epithelia. Its reactivity with precancerous lesions of CIN (Stages I-III) is approximately 30% positive. Molecular weight and other characteristics of the MAb 17.13'antigen. . . by Holfhofer, et
al., Lab, Invest. 49: 317 (1983) and product inserts of LabSystems, Inc. (Chicago, Illinois) for MAbs PKK1 and PKK2, These **antibodies**, respectively, recognize the PKK1 antigen which is a cytokeratin (Mr 41 KDI 45 KDI 48 kD and 56 kD) and the PKK2. . . available. MAb
PKK1 binds to all layers of stratified epithelia. PKK2 reportedly (according to Intek) binds to basal and parabasal

layers of stratified **squamous** epithelia as well as **columnar** epithelium of the normal lung. MAb PKK2 binds to SCCs,, but also binds to bronchioalveolar carcinoma, MAb PKK1 binds to all layers of. . . epithelia and reacts with a broad range of cytokeratins. MAb PKK2 also shows broad reactivity in that it is reactive with normal **columnar** epithelium (lung) as well as stratified epithelium. Thus., it fails to distinguish stratified **squamous** epithelia from other types of epithelia.

ACCESSION NUMBER: 548070 EUROPATFULL EW 199732 FS PS
TITLE: MONOCLONAL ANTIBODY FOR DIFFERENTIATION OF SQUAMOUS CELL

CARCINOMA ANTIGENS AND METHOD OF USE FOR SAME.
MONOKLONALER ANTIKOeRPER ZUR DIFFERENZIERUNG VON "SQUAMOUS CELL CARCINOMA"-ANTIGENEN UND VERFAHREN ZU DESSEN VERWENDUNG.
ANTICORPS MONOCLONAL POUR LA DIFFERENCIATION D'ANTIGENES

DE CARCINOMES DE CELLULES SQUAMEUSES ET PROCEDE D'UTILISATION.

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PATENT ASSIGNEE(S): BIOMIRA, INC., 9411 - 20 Avenue, Edmonton Alberta T6N 1E5, CA
PATENT ASSIGNEE NO: 1065742
AGENT: Andersen, Henrik Rastrup et al, c/o Plougmann & Vingtoft

A/S, Sankt Annae Plads 11, P.O. Box 3007, 1021 Copenhagen K, DK
AGENT NUMBER: 60641

OTHER SOURCE: EPB1997051 EP 0548070 B1 970806
SOURCE: Wila-EPS-1997-H32-T1
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES: R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R IT; R LI; R LU; R NL; R SE
PATENT INFO.PUB.TYPE: EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)

PATENT INFORMATION:

PATENT NO	KIND	DATE
EP 548070	B1	19970806
'OFFENLEGUNGS' DATE:		19930630
APPLICATION INFO.:	**EP 1990-907691**	**19900420**
PRIORITY APPLN. INFO.:	US 1989-341402	19890421
RELATED DOC. INFO.:	WO 90-US2152	900420 INTAKZ
	WO 9012885	901101 INTPNR

REF. NON-PATENT-LIT.: DIFFERENTIATION, vol. 31, 1986, Springer-Verlag, Berlin (DE); M. HUSZAR et al., pp. 141-153 # CANCER RESEARCH, vol. 47, no. 12, 15 June 1987, Philadephia, PA (US);

D.A. JOHNSON etal., pp. 3118-3122 JOHNSON et al., pp. 3118-3122 CANCER RESEARCH, vol., 49, no. 9, 01 May 1989,

Philadelphia, PA, US); J. SAMUEL et al., pp. 2465-2470 BIOSIS, AN no. 88.477505, J. Samuel et al.: "Novel squamous cell carcimona differentiation antigens recognized by MAb 174H.64", see abstract T115

AI **EP 1990-907691** **19900420**

DETDEN. . . al., Lab. Invest. 49: 317 (1983) and product inserts of LabSystems, Inc. (Chicago, Illinois) for MAbs PKK1 and PKK2. These **antibodies**, respectively, recognize the PKK1 antigen which is a cytokeratin (Mr 41 KD, 45 KD, 48 kD and 56 kD) and. . . binds to all layers of stratified epithelia. PKK2 reportedly (according to Intek) binds to basal and parabasal layers of stratified **squamous** epithelia as well as **columnar** epithelium of the normal lung. MAb PKK2 binds to SCCs, but also binds to bronchioalveolar carcinoma. MAb PKK1 binds to. . . reacts with a broad range of cytokeratins.

MAb

PKK2 also shows broad reactivity in that it is reactive with normal **columnar** epithelium (lung) as well as stratified epithelium. Thus, it fails to distinguish stratified **squamous** epithelia from other types of epithelia. Besides, its tumor reactivity also lacks specificity in that it reacts with lung tumors. . .

09/230955

L6 ANSWER 1 OF 2 MEDLINE on STN
ACCESSION NUMBER: 83281775 MEDLINE
DOCUMENT NUMBER: 83281775 PubMed ID: 6882017
TITLE: Measurement of urinary neopterin in normal pregnant and non-pregnant women and in women with **benign** and **malignant** genital tract **neoplasms**.
AUTHOR: Bichler A; Fuchs D; Hausen A; Hetzel H; Reibnegger G; Wachter H
SOURCE: ARCHIVES OF GYNECOLOGY, (1983) 233 (2) 121-30. Journal code: 7901051. ISSN: 0170-9925.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198309
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19980206
Entered Medline: 19830923

AB Urinary neopterin was measured in healthy women (n = 209) and men (n = 208), in patients with benign gynecological tumors (n = 53), in women with precancerous lesions of the **cervix** and the endometrium (n = 24) and in women with cancer of the genital tract (n = 108). In addition urinary neopterin measurements were made in 109 pregnant women and 20 women in the puerperium. No significant difference was found between mean neopterin values in patients with benign gynecological tumors, in women with precancerous lesions and in healthy women. Patients with cancer had significantly higher mean urinary neopterin levels than the control group. Raised neopterin levels were found in 56% of patients with genital tract cancer, the figures varying between 93% for ovarian cancer and 47% for cancer of the **cervix**. Some of the cancer patients had serial urinary neopterin measurements and in about 80% there was some relation between urinary neopterin values and clinical progress as judged clinically and radiologically, the best agreement existing in patients with ovarian cancer. Significantly higher mean neopterin values were found during normal pregnancy and in the early puerperium than in non-pregnant healthy controls. Raised urinary neopterin excretion may be due to enhanced cell proliferation and alloantigenic activation of T-lymphocytes.

L24 ANSWER 3 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 90383550 MEDLINE
DOCUMENT NUMBER: 90383550 PubMed ID: 2205681
TITLE: Establishment of hybridomas secreting monoclonal antibodies to placental alkaline phosphatase and development of an enzyme immunoassay for its determination.
AUTHOR: Kinoshita Y; Okamoto T; Mano H; Furuhashi Y; Goto S; Tomoda Y
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Nagoya University School of Medicine.
SOURCE: NIPPON SANKA FUJINKA GAKKAI ZASSHI. ACTA OBSTETRICA ET GYNAECOLOGICA JAPONICA, (1990 Jun) 42 (6) 613-9.
Journal code: 7505749. ISSN: 0300-9165.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901122
Last Updated on STN: 19901122
Entered Medline: 19901023

AB We established seven hybridomas secreting murine IgG monoclonal antibodies (MoAbs) to placental alkaline phosphatase (PLAP). The seven hybridomas were designated (1) 7C6, (2) 6G10, (3) 5B9, (4) 6D5, (5) **6B5**, (6) 11G6 and (7) 3E10, respectively. The characteristics of these hybridomas were evaluated by radioimmunoassay (RIA) with 125I-PLAP. Their reactivity with the intestinal alkaline phosphatase, one of the alkaline phosphatase isozymes, was (1) 0.04, (2) 0.2, (3) 1.4, (4) 1.8, (5) 0, (6) 4.0 and (7) 6.2(%), respectively. None of them showed signs of cross-reactivity with the liver-type alkaline phosphatase, also one of the alkaline phosphatase isozymes, within a PLAP concentration of 2,000 IU/l. The subtype of 5B9 was IgG1, and that of the others was IgG2a. We then used 7C6, to develop a sensitive, specific and convenient enzyme immunoassay (EIA) for the determination of PLAP, and assayed sera from patients with various gynecologic diseases. The incidence of increased PLAP was 6.4% in patients with benign diseases, 21.5% in **cervical** cancer, 36.4% in endometrial carcinoma, and 39.5% in malignant ovarian tumors. The specificity for malignant diseases seemed to be higher than that of CA125. Among endometrial carcinomas, well-differentiated adenocarcinoma had the highest incidence of an increased concentration. Among malignant ovarian tumors, serous cystadenocarcinoma, endometrioid carcinoma, dysgerminoma and Krukenberg's tumor showed a higher incidence than the other types.

L22 ANSWER 6 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:360835 BIOSIS
DOCUMENT NUMBER: PREV199497373835
TITLE: In vitro and in vivo analysis of cellular origin of **cervical** squamous metaplasia.
AUTHOR(S): Tsutsumi, Kouichiro; Sun, Qi; Yasumoto, Shigeru; Kikuchi, Keiji; Ohta, Yujiro; Pater, Alan; Pater, Mary M. (1)
CORPORATE SOURCE: (1) Basic Med. Sci., Fac. Med., Memorial Univ. Newfoundland, St. John's, NF A1B 3V6 Canada
SOURCE: American Journal of Pathology, (1993) Vol. 143, No. 4, pp. 1150-1158.
ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have previously shown that cultured normal human endocervical cells (HENs) form epithelium resembling **squamous** metaplasia in vivo. To analyze the cellular origin of **squamous** metaplasia, the cytokeratin and mucin expression and morphological features of HENs in monolayer cultures and in implants beneath the skin of nude mice were examined. Primary HENs had two distinct morphological phenotypes in vitro:pleomorphic epithelial cells and keratinocyte like cells. Using a panel of monoclonal **antibodies** for various cytokeratins (CKs), we observed that the pleomorphic cells, which were the primary outgrowths, expressed CK7 and CK18 and produced mucin, suggesting their origin to be the mucosecretory **columnar** cells (CCs) of the endocervix. Keratinocyte like cells were observed in proximity of the CC-like cells after a few days of HEN culture. Interestingly, these cells were homogeneously negative for CK7 expression, as for native reserve cells (RCs), and homogeneously positive for CK13 expression with the **antibody** that is specific for RCs. During early passages, the culture consisted mostly of the RC-like keratinocytelike cells, and in the late passages, the CC-like cells were predominant. HEN implants in nude mice morphologically formed epithelia similar to immature **squamous** metaplasia and showed variable CK18 expression. Moreover, they showed homogeneous CK13 expression throughout all layers and expressed mucin and CK7 in the suprabasal cells. The possibility that the HEN culture was originally a mixed population of CCs and RCs, that we failed to detect, cannot be eliminated Our results support the more likely view that the endocervical simple epithelia, which form **squamous** metaplasia, are bipotential cells and undergo differentiation readily and reversibly to give rise to CC-like and RC-like cells in culture.

L22 ANSWER 7 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
ACCESSION NUMBER: 1993:228547 BIOSIS
DOCUMENT NUMBER: PREV199395119722
TITLE: Expression of keratins 1, 6, 15, 16, and 20 in normal **cervical** epithelium, squamous metaplasia, **cervical** intraepithelial neoplasia, and **cervical** carcinoma.
AUTHOR(S): Smedts, Frank (1); Ramaekers, Frans; Leube, Rudolf E.; Keijser, Karel; Link, Monique; Vooijs, Peter
CORPORATE SOURCE: (1) Dep. Pathology, Diagnostic Centre S.S.D.Z. Reinier De Graafweg 7, 2600 GA Delft, The Netherlands
SOURCE: American Journal of Pathology, (1993) Vol. 142, No. 2, pp. 403-412.
ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Expression of keratins 1, 6, 15, 16, and 20 was examined in normal **cervical** epithelia, **squamous** metaplasia, various grades of **cervical** intraepithelial neoplasia, and both **squamous** cell carcinomas and adenocarcinomas of the **cervix** with monospecific **antibodies**. Ectocervical epithelium contains all of these keratins except keratin 20. They show a heterogeneous distribution, with a basally restricted detection of keratin 15. Endocervical **columnar** cells were found to contain significant amounts of keratin 16, whereas the subcolumnar reserve cells expressed considerable amounts of keratin 15 and 16, and frequently keratin 6. These reserve cell keratins were also found in immature and mature **squamous** metaplastic epithelium. In the **cervical** intraepithelial neoplastic lesions they were generally found with increasing intensity as the severity of the lesion progressed. In the keratinizing variety of **squamous** cell carcinoma of the **cervix**, these three keratins seem to constitute an important part of the intermediate filament cytoskeleton, whereas in nonkeratinizing **squamous** cell carcinoma, they occur to a much lesser extent. Surprisingly, these keratins were also occasionally found in adenocarcinomas. From these data we conclude that the keratin phenotype of reserve cells and endocervical **columnar** cells is more complex than previously suggested. In particular, the keratins occurring in reserve cells are also present in most of the premalignant and in a considerable number of the malignant lesions of the **cervix**. The differentiation features of the various carcinoma types are, however, reflected in their specific keratin filament composition.

L22 ANSWER 9 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5

ACCESSION NUMBER: 1992:125114 BIOSIS
DOCUMENT NUMBER: BA93:70914
TITLE: PATTERNS OF KERATIN SUBSETS IN NORMAL AND ABNORMAL UTERINE **CERVICAL** TISSUES AN IMMUNOHISTOCHEMICAL STUDY.
AUTHOR(S): MALECHA M J; MIETTINEN M
CORPORATE SOURCE: DEP. PATHOL. CELL BIOL., THOMAS JEFFERSON UNIV. HOSP., NEW HOSP., ROOM 6208, 111 SOUTH 11TH ST., PHILDELPHIA, PA. 19107-5098, USA.
SOURCE: INT J GYNECOL PATHOL, (1992) 11 (1), 24-29.
CODEN: IJGPDR.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB We investigated the use of three monoclonal antikeratin **antibodies** on routinely formalin-fixed and paraffin-embedded punch and cone biopsies of the normal human uterine **cervix** and its metaplastic and premalignant lesions. Monoclonal **antibodies** used were AE8, which is specific for keratin 13; 34BE12, which reacts with keratins of the stratified **squamous** epithelium; and CAM5.2, which is specific for keratin 8. All these **antibodies** performed well in routinely processed surgical pathology material. AE8 **antibody** stained the suprabasal layer of the normal **squamous** epithelium. **Squamous** metaplasia and dysplasia were stained in 50% of the cases. Normal suprabasal distribution of the keratin 13, however, was lost in all positive dysplasia cases. CAM5.2 reacted with normal **columnar** cells in all cases, and **squamous** metaplasia was focally positive in 20% of the cases. Dysplasia showed a positive reaction in 30% to 40% of the cases. The 34BE12 **antibody** was reacting with the full thickness of the **squamous** epithelium. **Squamous** metaplasia and dysplasia were positive in 80% of the cases. In addition, 34BE12 stained reserve cell hyperplasia, making it a useful marker for this condition. Our results demonstrate that keratin immunohistochemistry with the above-listed **antibodies** gives pathogenetically interesting information on **cervical** lesions.

L22 ANSWER 15 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:286993 BIOSIS
DOCUMENT NUMBER: BA90:17839
TITLE: IMMUNOHISTOCHEMICAL IDENTIFICATION OF RESERVE CELLS OF THE ENDOCERVICAL CANAL BY MONOCLONAL ANTIBODIES EE-21-06D.
AUTHOR(S): RAIKHLIN N T; DOBRYNIN V A; PETROV S V; SERRE D
CORPORATE SOURCE: ALL-UNION ONCOL. SCI. CENT., MOSCOW, USSR.
SOURCE: BYULL EKSP BIOL MED, (1989) 108 (11), 603-606.
CODEN: BEBMAE. ISSN: 0365-9615.
FILE SEGMENT: BA; OLD
LANGUAGE: Russian

AB Expression of cytokeratin polypeptides characteristic of **squamous** epitelium was studied in reserve cells of **cervical** canal obtained from 8 women by the more immunofluorescence method with the help of monoclonal **antibodies** EE21-06d /MAB/. MAB EE21-06d were shown to detect individual reserve cells as well as their hyperplasia foci without staining **columnar** cells.

L22 ANSWER 16 OF 29 CANCERLIT
ACCESSION NUMBER: 89328031 CANCERLIT
DOCUMENT NUMBER: 89328031 PubMed ID: 2474040
TITLE: The production and characterization of monoclonal antibody,
1C5, reactive with **cervical** adenocarcinoma of the uterus.
AUTHOR: Koizumi M; Uede T; Kudo R
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Sapporo Medical College.
SOURCE: NIPPON SANKA FUJINKA GAKKAI ZASSHI. ACTA OBSTETRICA ET GYNAECOLOGICA JAPONICA, **(1989 May)** 41 (5) 530-6.
Journal code: 7505749. ISSN: 0300-9165.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 89328031
ENTRY MONTH: 198909
ENTRY DATE: Entered STN: 19941107
Last Updated on STN: 19970509

AB A new monoclonal **antibody**, 1C5, was produced by fusion of spleen cells obtained from mice immunized with CAC-1, a human cell line of **cervical** adenocarcinoma of the uterus, and NS-1 myeloma cell. The objectives of this study were to obtain moAb that can be used for routine histology and cytology, and to examine the histogenesis of **cervical** adenocarcinoma. 1. 1C5 reacted with 88% of **cervical** adenocarcinoma of the uterus, but did not react with **cervical squamous** cell carcinoma of the uterus and other **squamous** cell carcinoma. However, 1C5 reacted with some adenocarcinomas, such as endometrial carcinoma of the uterus and ovarial carcinoma. 2. The staining pattern by 1C5 was different, in **cervical** adenocarcinoma from that in endometrial carcinoma of the uterus, and also different in the endocervical type from that in the endometrioid type of **cervical** adenocarcinoma. Therefore, 1C5 is useful in distinguishing between two types of adenocarcinoma of the uterus. 3. 1C5 did not react with normal **squamous** cells or normal **columnar** cells of the uterine **cervix**, or with normal endometrial cells of the uterus. However, the **columnar** cells in a limited area of the **squamocolumnar** junction were strongly stained with 1C5. 4. 1C5 reacted with ethanol-fixed, and routine formalin-fixed and paraffin-embedded tissue. Thus, 1C5 may be used for clinical diagnosis. 5. 1C5 was found to be IgG1. 6. The molecular weight of the 1C5-defined antigen was 26,000 daltons, and the epitope of the 1C5-defined antigen was carbohydrate moiety. 7. We examined the histogenesis of **cervical** adenocarcinoma of the uterus by utilizing the reactivity of 1C5.(ABSTRACT TRUNCATED AT 250 WORDS)

L22 ANSWER 20 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:246953 BIOSIS
DOCUMENT NUMBER: BA87:128018
TITLE: SUBTYPING OF EPITHELIAL CELLS OF NORMAL AND METAPLASTIC HUMAN UTERINE **CERVIX** USING POLYPEPTIDE-SPECIFIC CYTOKERATIN ANTIBODIES.
AUTHOR(S): LEVY R; CZERNOBILSKY B; GEIGER B
CORPORATE SOURCE: DEP. CHEMICAL IMMUNOL., WEIZMANN INST. SCI., REHOVOT, ISRAEL.
SOURCE: DIFFERENTIATION, (1988) 39 (3), 185-196.
CODEN: DFFNAW. ISSN: 0301-4681.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The aim of the present study was to explore the histogenesis of metaplastic cells in the human uterine **cervix**. In a previous study [20] we demonstrated that **squamous cervical** metaplasia expresses a unique set of cytokeratin polypeptides different from that expressed by the various normal epithelial elements of both the exo- and endocervix. It was thus proposed that the formation of **squamous** metaplasia represented a new route of differentiation. In the present study we further investigated this aspect by expanding the battery of monoclonal **antibodies** directed against specific cytokeratin epitopes used for **immunohistochemical** labelling. The **antibodies** used were: KS-1A3, which specifically stains cytokeratin polypeptide no. 13; **antibody** KS-2.1, which is an anti-cytokeratin reacting with pseudostratified transitional and some simple epithelia; and **antibody** KS-B17.2 reacting with cytokeratin polypeptide no. 18. Examination of the staining patterns obtained with these **antibodies** revealed specific staining of ciliated cells with **antibody** KS-2.1 and of endocervical reserve cells with **antibody** KS-1A3. In 6 out of 19 cases tested reserve cells were also stained with **antibody** KS-2.1. These results enabled us to distinguish between at least four types of cells residing within the simple epithelium of the endocervix, namely **columnar** nonciliated cells, ciliated cells, and two subpopulations of reserve cells. Since metaplasia was positively stained by **antibodies** KS-1A3 and KS-2.1, we propose that the endocervical reserve cells that express cytokeratin polypeptide no. 13 are most probably the cells from which endocervical metaplasia is derived.

L22 ANSWER 21 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1988:223517 BIOSIS
DOCUMENT NUMBER: BA85:112752
TITLE: IMMUNOPHENOTYPIC ANALYSIS OF THE TRANSFORMATION ZONE OF HUMAN **CERVIX**.
AUTHOR(S): RONCALLI M; SIDERI M; GIE P; SERVIDA E
CORPORATE SOURCE: SERVIZIO ANATOMIA ISTOLOGIA PATOLOGICA, OSPEDALE FATEBENEFRATELLI OFTALMICO, CORSO PORTO NUOVA, 23, 20121, MILANO, ITALIA.
SOURCE: LAB INVEST, (1988) 58 (2), 141-149.
CODEN: LAINAW. ISSN: 0023-6837.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The immunocompetent cell population of the **cervical** transformation zone of 18 uteri removed for noncervical disease, has been investigated with monoclonal **antibodies**. The panel included Leu 2a, 3a, 4, 14, and IL II receptor for lymphocytes and T cell subsets, Leu 7 for NK cells, Leu M5, Leu 10, HLA-DR, DRC 1 for dendritic cells, and Leu 6 for Langerhans' cells (LC). In ectocervical epithelium HLA-DR, Leu 6 and Leu 10 **antibodies** identified subpopulations of dendritic cells which differed in number and in topographic distribution. Furthermore, a strong HLA-DR epithelial positivity was constantly observed in endocervical **columnar** cells as well as in keratinocytes of **squamous** metaplasia. Leu 2a+ cells (T suppressor/cytotoxic) prevailed in the stromal and epithelial compartments of ecto/endocervix; in 6 cases, however, Leu 3a+ cells (T helper/inducer) represented the main T cell subset in the ectocervical stroma. B lymphocytes were occasionally noticed in the subepithelial stroma while NK and DRC-1 cells were never observed. Finally, only few lymphocytes displayed a positivity for IL II receptor. This study suggests that several phenotypes of intraepithelial dendritic cells are present in the transformation zone and that endocervical **columnar** cells and keratinocytes of **squamous** metaplasia express HLA-DR products; the latter finding may be related to the presence of intraepithelial and stromal T lymphocytes.

12

ACCESSION NUMBER: 1987:5455 BIOSIS
DOCUMENT NUMBER: BA83:5455
TITLE: CYTOKERATIN EXPRESSION IN SQUAMOUS METAPLASIA OF THE HUMAN UTERINE **CERVIX**.
AUTHOR(S): GIGI-LEITNER O; GEIGER B; LEVY R; CZERNOBILSKY B
CORPORATE SOURCE: DEP. CHEM. IMMUNOL., WEIZMANN INST. SCI. REHOVOT, ISRAEL.
SOURCE: DIFFERENTIATION, (1986) 31 (3), 191-205.
CODEN: DFFNAW. ISSN: 0301-4681.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The expression of cytokeratin polypeptides in **squamous** metaplasia of the human uterine **cervix** was investigated by immunocytochemical labeling with polypeptide-specific **antibodies** against cytokeratins. Immunofluorescence microscopic examination of **cervical** tissues using various monoclonal **antibodies** indicated that **squamous cervical** metaplasia expresses a unique set of cytokeratin polypeptides, this being distinctively different from that expressed by all of the normal epithelial elements of the exoand endocervix. The development of metaplastic foci was accompanied by the expression of cytokeratin polypeptide no. 13, which is commonly detected in stratified epithelia, and by a reduction in the level of polypeptide no. 18, which is typical of simple epithelia. The 40-kilodalton cytokeratin (no. 19) described by Moll et al., which is abundant in the **columnar** and reserve cells of the endocervix, was found throughout the metaplastic lesions. Only in 'well-differentiated' metaplasias did we detect polarity of cytokeratin expression reminiscent of the staining patterns in the exocervix. This was manifested by the exclusive labeling of the basal cell layer(s) with **antibodies** KB 8.37 and KM 4.62, which stain the basal cells of the exocervix. Furthermore, a comparison of **cervical** metaplasia with **squamous** areas occurring within endometrial adenocarcinomas pointed to a close similarity in the cytokeratin expression of the two. We discuss the use of cytokeratins as specific markers of **squamous** differentiation, the relationships between **squamous** metaplasia and **cervical** neoplasia, and the involvement of reserve cells in the metaplastic process.

L22 ANSWER 24 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13

ACCESSION NUMBER: 1986:324562 BIOSIS
DOCUMENT NUMBER: BA82:48867
TITLE: IMMUNOHISTOCHEMICAL IDENTIFICATION OF LANGERHANS CELLS IN NORMAL EPITHELIUM AND IN EPITHELIAL LESIONS OF THE UTERINE **CERVIX**.
AUTHOR(S): PUTS J J G; MOESKER O; DE WAAL R M W; KENEMANS P; VOOIJS G P; RAMAEKERS F C S
CORPORATE SOURCE: DEPT. OF PATHOLOGY, UNIVERSITY OF NIJMEGEN, GEERT GROOTENPLEIN ZUID 24, 6525 GA NIJMEGEN, NETHERLANDS.
SOURCE: INT J GYNECOL PATHOL, (1986) 5 (2), 151-162.
CODEN: IJGPDR.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Using the double label indirect immunofluorescence technique we have studied vimentin-positive cells present in normal ecto- and endocervical epithelium, subcolumnar reserve cell hyperplasia, and **squamous** metaplastic and dysplastic epithelium of the uterine **cervix**. Monoclonal **antibodies** to Ia- and T6-antigens were applied in the examination of the expression of these membrane markers by such cells. Our studies reveal the presence of a relatively large number of vimentin-positive and T6-positive (Langerhans) cells in normal ectocervical stratified **squamous** epithelium, a small number in endocervical **columnar** epithelium, and a larger number in subcolumnar reserve cell hyperplasia and in immature **squamous** metaplasia. In this respect, mature **squamous** metaplastic epithelium shows a great resemblance to normal ectocervical stratified **squamous** epithelium. In contrast with previous reports in the literature we could only demonstrate small numbers of Langerhans cells in cases of dysplasia. The clinicopathological significance of these findings is discussed.

L22 ANSWER 25 OF 29 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 86110751 MEDLINE
DOCUMENT NUMBER: 86110751 PubMed ID: 2417968
TITLE: Expression of cytokeratins in early neoplastic epithelial lesions of the uterine **cervix**.
AUTHOR: Puts J J; Moesker O; Kenemans P; Vooijs G P; Ramaekers F C
SOURCE: INTERNATIONAL JOURNAL OF GYNECOLOGICAL PATHOLOGY, **(1985)** 4 (4) 300-13. Ref: 55
Journal code: 8214845. ISSN: 0277-1691.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860228

AB Polyclonal and monoclonal antibodies to cytokeratin polypeptides were used to study the expression of these intermediate filament proteins in normal, squamous metaplastic, and neoplastic epithelium of the uterine **cervix**, in order to investigate the morphogenesis of early epithelial changes preceding **cervical** squamous cell carcinoma. A polyclonal keratin antiserum showed a positive reaction in all different epithelial cell types of the uterine **cervix**. A positive reaction was also found in subcolumnar reserve cell hyperplasia, in squamous metaplastic and dysplastic cells, and in (squamous) carcinoma in situ. A monoclonal **antibody** specific for **columnar** epithelium (RGE 53) gave a positive reaction in endocervical **columnar** cells and in some immature metaplastic cells but was negative in subcolumnar reserve cells, **squamous** (metaplastic) cells, dysplastic cells, and most cases of carcinoma in situ. Another monoclonal cytokeratin antibody (RKSE 60) pointed to early keratinization in light microscopically nonkeratinizing squamous (metaplastic) and dysplastic epithelium. A possible overlap in staining patterns of RGE 53 and RKSE 60 was seen in some cases of immature metaplasia. Morphologic changes occurring in the transformation zone upon dedifferentiation are accompanied by alterations in cytokeratin expression. Similarities in cytokeratin expression were found between dysplasia and carcinoma in situ on one hand and subcolumnar reserve cell hyperplasia and squamous metaplasia on the other. This study favors an epithelial origin and a squamoid nature of subcolumnar reserve cells.

L22 ANSWER 26 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 15

ACCESSION NUMBER: 1984:284238 BIOSIS
DOCUMENT NUMBER: BA78:20718
TITLE: SKIN CALCIUM BINDING PROTEIN IN SQUAMOUS METAPLASIA OF HUMAN UTERINE **CERVIX**.
AUTHOR(S): PAVLOVITCH J H; DELEZOIDE A L; DIDIERJEAN L; SAURAT J H; PFISTER A
CORPORATE SOURCE: HOPITAL DES ENFANTS-MALADES, TOUR TECHNIQUE 6EME ETAGE, 149, RUE DE SEVRES, 75743 PARIS CEDEX 15.
SOURCE: AM J PATHOL, (1984) 114 (3), 454-460.
CODEN: AJPAA4. ISSN: 0002-9440.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The distribution of skin Ca-binding protein [SCaBP] in **squamous** cell metaplasia of human endocervix, in normal human skin, and in ovarian cancer was determined by the immunofluorescence technique. A rabbit antiserum specific to rat SCaBP was characterized by Ouchterlony immunodiffusion and by immunoprecipitation of 125I-labeled SCaBP. The specificity of **antibody** labeling was demonstrated by using preimmune rabbit serum and SCaBP antiserum competitively absorbed with purified SCaBP. In normal human skin SCaBP was found exclusively in the basal layer cell cytoplasm. This protein was not detected in normal **columnar** epithelium of endocervix. Epithelial tissues in the zone of transition between the cylindrical epithelium of the endocervical mucosa and the stratified **squamous** epithelium of the exocervix were obtained from 14 patients with a wide variety of **squamous** cell metaplasias. In the early stage of metaplasia SCaBP was detected exclusively in the cytoplasm of reserve undifferentiated cells. In the terminal stage of metaplasia the SCaBP was present only in the basal cell layer. SCaBP was found in several layers of dysplastic tissue, and this distribution appeared to be related to the loss of normal maturation of the epithelium. SCaBP was also present in **squamous** cell carcinoma of endocervix, especially in the least differentiated regions of the tumor. No SCaBP was detected in any ovarian cancer cells. These findings are potentially useful as a means of early detection of **squamous** metaplasia and of distinguishing premalignant anaplastic lesions from those that are benign and non-proliferative. In addition, the presence of SCaBP in tumors derived from metaplastic epithelia and its absence in the ovarian cancer indicate that **immunohistochemical** search for this protein might be of value in tumors in which an epidermoid origin is a possibility.

L22 ANSWER 27 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
16

ACCESSION NUMBER: 1982:261010 BIOSIS
DOCUMENT NUMBER: BA74:33490
TITLE: BASEMENT MEMBRANE OF THE UTERINE **CERVIX** IMMUNO FLUORESCENCE CHARACTERISTICS OF THE COLLAGEN COMPONENT IN NORMAL OR ATYPICAL EPITHELIUM AND INVASIVE CARCINOMA.
AUTHOR(S): FRAPPART L; BERGER G; GRIMAUD J A; CHEVALIER M; BREMOND A; ROCHET Y; FEROLDI J
CORPORATE SOURCE: LABORATOIRE D'ANATOMIE PATHOLOGIQUE, U.E.R. GRANGE-BLANCHE 8, AVENUE ROCKEFELLER, 69373 LYON CEDEX 2, FRANCE.
SOURCE: GYNECOL ONCOL, (1982) 13 (1), 58-66.
CODEN: GYNOA3. ISSN: 0090-8258.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Frozen sections of the [human] uterine **cervix** were processed by an indirect immunofluorescence technique using specific antisera against type I, III and IV collagens (raised in rabbits). A continuous basement membrane (BM) was selectively stained using **antibodies** against type IV collagens beneath **squamous** and **columnar** epithelia. In the case of atypical epithelium, the appearance of BM beneath the epithelia remains unchanged. With invasive carcinomas, a more or less continuous band of unequal thickness, whose reactivity in the presence of **antibodies** to type IV collagen remains weak or moderate, is observed around the lobules of neoplastic cells. The unimpaired character of the basement membrane cannot be considered as the major criterion, to distinguish carcinoma in situ from invasive carcinoma of the uterine **cervix**.

L22 ANSWER 28 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1980:211313 BIOSIS
DOCUMENT NUMBER: BA70:3809
TITLE: IMMUNO HISTOCHEMICAL LOCALIZATION OF KERATIN IN NORMAL HUMAN TISSUES.
AUTHOR(S): SCHLEGEL R; BANKS-SCHLEGEL S; PINKUS G S
CORPORATE SOURCE: DEP. PATHOL., PETER BENT BRIGHAM HOSP., 721 HUNTINGTON AVE., BOSTON, MASS. 02115, USA.
SOURCE: LAB INVEST, (1980) 42 (1), 91-96.
CODEN: LAINAW. ISSN: 0023-6837.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB **Immunohistochemical** identification of intracellular keratin was achieved using an indirect **antibody** technique on paraffin-embedded human tissue. A study of numerous tissues confirms that keratins are abundant in all layers of **squamous** epithelia, in the ducts of epithelial-derived glands and in the epithelia of the respiratory and urinary tracts. By using an immunoperoxidase technique which offers increased histologic resolution, the basal or reserve cells of the tracheal, bronchial, prostatic and **cervical** gland epithelia are shown to be the predominant keratin-containing cells in these tissues. The normal differentiation of basal cells into nondividing, superficial **columnar** cells is accompanied by the loss of cytoplasmic keratin proteins. Foci of epithelial **squamous** metaplasia stain intensely with antikeratin **antibodies** and presumably represent an exaggerated proliferation of the keratin-containing basal cells. Alveolar respiratory epithelium, acinar cells of various glands and many mesodermal tissues (muscle, hematopoietic and lymphoid tissue, nerve and connective tissue) were devoid of keratin proteins. The ability to identify keratin proteins within fixed, embedded tissue (including those known to lack tonofilament bundles) may be useful in the study of tissue histogenesis and carcinogenesis and in the pathologic assessment of poorly differentiated malignant neoplasms and tumors of controversial cellular origin.

L22 ANSWER 29 OF 29 CANCERLIT
ACCESSION NUMBER: 80663776 CANCERLIT
DOCUMENT NUMBER: 80663776
TITLE: IMMUNOHISTOCHEMICAL LOCALIZATION OF KERATIN IN NORMAL HUMAN
TISSUES.
AUTHOR: Schlegel R; Banks-Schlegel S; Pinkus G S
CORPORATE SOURCE: Dept. Pathology, Peter Bent Brigham Hosp., Harvard Medical Sch., Boston, MA, 02115.
SOURCE: Non-serial, **(1980)** Non-serial; 42(1):91-96 1980 .
ISSN: 0023-6837.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 198007
ENTRY DATE: Entered STN: 19941107
Last Updated on STN: 19960517

AB **Immunohistochemical** identification of intracellular keratin was achieved using an indirect **antibody** technique on paraffin-embedded human tissue. A study of numerous tissues confirms that keratins are abundant in all layers of **squamous** epithelia, in the ducts of epithelial-derived glands, and in the epithelia of the respiratory and urinary tracts. Using an immunoperoxidase technique which offers increased histologic resolution, we have shown that the basal or reserve cells of the tracheal, bronchial, prostatic, and **cervical** gland epithelia are the predominant keratin-containing cells in these tissues. The normal differentiation of basal cells into nondividing, superficial **columnar** cells is accompanied by the loss of cytoplasmic keratin proteins. Foci of epithelial **squamous** metaplasia stain intensely with antikeratin **antibodies** and presumably represent an exaggerated proliferation of the keratin-containing basal cells. Alveolar respiratory epithelium, acinar cells of various glands, and many mesodermal tissues (muscle, hematopoietic, and lymphoid tissue, nerve, and connective tissue) were devoid of keratin proteins. The ability to identify keratin proteins within fixed, embedded tissue (including those known to lack tonofilament bundles) may prove useful in the study of tissue histogenesis and carcinogenesis, and in the pathologic assessment of poorly differentiated malignant neoplasms and tumors of controversial cellular origin. (Author abstract) (30 Refs)

L10 ANSWER 1 OF 6 MEDLINE
ACCESSION NUMBER: 96424909 MEDLINE
DOCUMENT NUMBER: 96424909 PubMed ID: 8827360
TITLE: Expression of the MN antigen in cervical papanicolaou smears is an early diagnostic biomarker of cervical dysplasia.
AUTHOR: Liao S Y; Stanbridge E J
CORPORATE SOURCE: Department of Medicine, University of California, College of Medicine, Irvine 92717, USA.
CONTRACT NUMBER: CA 19401 (NCI)
SOURCE: CANCER EPIDEMIOLOGY, BIOMARKERS AND PREVENTION, **(1996 Jul)** 5 (7) 549-57.
Journal code: 9200608. ISSN: 1055-9965.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961213

AB A new tumor-associated antigen, MN, has been shown to be expressed in virtually all cervical carcinomas and the majority of cervical intraepithelial neoplasia, but not in normal cervices (S. Y. Liao et al., Am. J. Pathol., 145: 598-609, 1994). Therefore, we postulated that the exfoliative cells in cervical Papanicolaou (Pap) smears would reflect the MN immunoreactivity seen in the tissue sections, and high levels of MN expression in the exfoliative cells would indicate the presence of dysplasia in the cervix. A total of 305 cervical Pap smears, with histological confirmation, representing all categories of the Bethesda System, were immunohistologically examined. We found that high levels of MN expression in exfoliative cells were not restricted to the dysplastic cells but were observed also in the normal endocervical cells (NECs) when dysplasia was present in the tissue biopsies. Overall, the rates of positive MN immunostaining of the dysplastic cells in low- and high-grade **squamous** intraepithelial lesions and invasive carcinoma were 35 (65%) of 54, 44 (77%) of 57, and 12 (92%) of 13, respectively. However, diffuse MN immunoreactivity of the atypical and/or dysplastic endocervical **columnar** cells was seen in all cases (100%) of adenocarcinoma in situ (AIS; n = 23) and adenocarcinomas (n = 8). In the groups with cytological diagnoses of atypical **squamous** cells or atypical glandular cells of undetermined significance (ASCUS and AGUS, respectively), MN positivity was seen in 47% of ASCUS (22/47) and 55% of AGUS (12/22). Dysplastic tissues were identified in all MN-positive cases. In contrast, all MN-negative atypical Pap smears were confirmed histologically to be benign cervix with one exception, in which the cytological diagnosis was ASCUS and focal low-grade **squamous** intraepithelial lesions were found in the cervix. The study also included 89 cases with cytological diagnoses of within normal limits/benign cellular changes. Among these, 10 Pap smears expressed diffuse MN antigen in the NEC, and dysplasia (8 cases of low-grade **squamous** intraepithelial lesions, 2 AIS) was found in the cervices. None of

MN-negative cases with "within normal limits" cytology contained dysplastic cervices. Therefore, it would seem that diffuse MN antigen expression in the NEC may be an indicator of cervical dysplasia. Thus, MN antigen might serve as an early biomarker of cervical neoplasia. The combination of detection via cytology and MN immunostaining resulted in no false negatives and also discriminated between cellular atypia due to benign reactive changes versus cellular atypia due to dysplasia in the category of ASCUS and AGUS. In particular, it was found in the AGUS group that diffuse MN immunostaining restricted to atypical **columnar** cells was diagnostic for AIS. These findings indicate that MN antigen expression is an important diagnostic biomarker of glandular neoplasia and a valuable adjunct to cytological diagnosis of ASCUS and AGUS.

L10 ANSWER 2 OF 6 MEDLINE
ACCESSION NUMBER: 93251452 MEDLINE
DOCUMENT NUMBER: 93251452 PubMed ID: 7683571
TITLE: Retinoid status controls the appearance of reserve cells and keratin expression in mouse cervical epithelium.
AUTHOR: Darwiche N; Celli G; Sly L; Lancillotti F; De Luca L M
CORPORATE SOURCE: Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, NIH, Bethesda, Maryland 20892.
SOURCE: CANCER RESEARCH, **(1993 May 15)** 53 (10 Suppl) 2287-99.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19960129
Entered Medline: 19930610

AB We describe an animal model to induce the histogenesis of **squamous** metaplasia of the cervical **columnar** epithelium, a condition usually preceding cervical neoplasia. This model is based on dietary retinoid depletion in female mice. Control sibling mice fed the same diet but with all-trans-retinoic acid (at 3 micrograms/g diet) showed the normal endocervical epithelial and glandular **columnar** morphology, typical of a simple epithelium without subcolumnar reserve cells. The stratified **squamous** ectocervical epithelium of these mice fed all-trans retinoic acid showed intense immunohistochemical staining in basal and suprabasal cells with mono-specific antibodies against keratins K5, K14, K6, K13, and, suprabasally, with antibodies specific for K1 and K10. At the **squamocolumnar** junction, the adjacent **columnar** epithelium (termed "suprajunctional") did not show staining for K5, K14, K6, K13, K1, and K10 but specifically stained for keratin K8, typical of simple epithelia and absent from the adjacent ectocervical **squamous** stratified lining (termed "subjunctional"), in striking contrast. Sections of the **squamocolumnar** junction from mice kept on the vitamin A-deficient diet for 10 weeks showed suprajunctional isolated patches of reserve cells, proximal and distal to the junction. These cells were detected prior to any symptoms of vitamin A deficiency, such as loss of body weight or respiratory discomfort. The subcolumnar reserve cells induced by vitamin A deficiency displayed positive staining for K5 and K14. As deficiency became severe, the reserve cells occupied the entirety of the suprajunctional basement membrane. This epithelium eventually became stratified and **squamous** metaplastic, the **squamocolumnar** junction was no longer discernible, and the entire endocervical epithelium and the endometrial glands lost K8 positivity, while acquiring K5, K14, K6, K13, K1, and K10 keratins typical of the ectocervix under normal conditions of vitamin A nutriture. Vitamin A deficiency also altered keratin expression and localization in **squamous** subjunctional epithelium. In situ hybridization studies for K1 and K5 mRNA showed their major site of expression at the basal (K5) and immediately suprabasal (K1)

cell layers. The localization of both K5 and K1 proteins in these same cell layers, and above, is consistent with transcriptional regulation of these keratins. Early vitamin A deficiency caused the appearance of single subcolumnar reserve cells expressing K5 mRNA. After these cells grew into a **squamous** focus, K1 mRNA became expressed suprabasally. We conclude that retinoid status plays a key role in maintaining differentiative characteristics of the cervical and glandular epithelia and, as such, may be a modulating factor in the development of cervical cancer.

L10 ANSWER 3 OF 6 MEDLINE
ACCESSION NUMBER: 93167343 MEDLINE
DOCUMENT NUMBER: 93167343 PubMed ID: 7679549
TITLE: Expression of keratins 1, 6, 15, 16, and 20 in normal cervical epithelium, **squamous** metaplasia, cervical intraepithelial neoplasia, and cervical carcinoma.
AUTHOR: Smedts F; Ramaekers F; Leube R E; Keijser K; Link M; Vooijs P
CORPORATE SOURCE: Department of Pathology, Diagnostic Centre S.S.D.Z. Delft, The Netherlands.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, **(1993 Feb)** 142 (2) 403-12.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930402
Last Updated on STN: 19960129
Entered Medline: 19930316

AB Expression of keratins 1, 6, 15, 16, and 20 was examined in normal cervical epithelia, **squamous** metaplasia, various grades of cervical intraepithelial neoplasia, and both **squamous** cell carcinomas and adenocarcinomas of the cervix with monospecific antibodies.

Ectocervical epithelium contains all of these keratins except keratin 20. They show a heterogeneous distribution, with a basally restricted detection of keratin 15. Endocervical **columnar** cells were found to contain significant amounts of keratin 16, whereas the subcolumnar reserve cells expressed considerable amounts of keratin 15 and 16, and frequently keratin 6. These reserve cell keratins were also found in immature and mature **squamous** metaplastic epithelium. In the cervical intraepithelial neoplastic lesions they were generally found with increasing intensity as the severity of the lesion progressed. In the keratinizing variety of **squamous** cell carcinoma of the cervix, these three keratins seem to constitute an important part of the intermediate filament cytoskeleton, whereas in nonkeratinizing **squamous** cell carcinoma, they occur to a much lesser extent. Surprisingly, these keratins were also occasionally found in adenocarcinomas. From these data we conclude that the keratin phenotype of reserve cells and endocervical **columnar** cells is more complex than previously suggested. In particular, the keratins occurring in reserve cells are also present in most of the premalignant and in a considerable number of the malignant lesions of the cervix. The differentiation features of the various carcinoma types are, however, reflected in their specific keratin filament composition.

L10 ANSWER 4 OF 6 MEDLINE
ACCESSION NUMBER: 92317750 MEDLINE
DOCUMENT NUMBER: 92317750 PubMed ID: 1619310
TITLE: Immunohistochemical study on the expression of E-cadherin in normal tissues and **squamous** cell carcinomas of the uterine cervix.
AUTHOR: Honda S
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Niigata University
School of Medicine.
SOURCE: NIPPON SANKA FUJINKA GAKKAI ZASSHI. ACTA OBSTETRICA ET GYNAECOLOGICA JAPONICA, **(1992 May)** 44 (5) 517-23.
Journal code: 7505749. ISSN: 0300-9165.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920815
Last Updated on STN: 19920815
Entered Medline: 19920731

AB The expression of epithelial cadherin (E-cadherin) was immunohistochemically analyzed in normal tissues and **squamous** cell carcinomas of the uterine cervix and investigated clinicopathologically in relation to factors including the histological type, clinical stage (FIGO), tumor invasion and lymph node metastasis. The following results were obtained. (1) In normal cervix, E-cadherin was found at the cell to cell borders in both **squamous** and **columnar** epithelia, but not in stromal tissues. (2) In 38 patients with cervical cancer, 6 patients exhibited homogeneous staining of E-cadherin, while 32 showed heterogeneous expression, suggesting that cell
to cell adhesion is not uniform in most cases. (3) In cases with large cell non-keratinizing **squamous** cell carcinoma invading to a depth exceeding 2/3 of the cervix, a significantly higher frequency of heterogeneous expression of E-cadherin was seen (p less than 0.05). (4) Patients who had cancer invasion exceeding 2/3 of the cervix with heterogeneous expression tended to have a high incidence of nodal metastasis. These results indicate that the expression of E-cadherin in cancer may be one of the factors most responsible for the process of invasion and metastasis in cervical cancer.

L27 ANSWER 5 OF 7 USPATFULL
ACCESSION NUMBER: 94:51330 USPATFULL
TITLE: Method of diagnosing the presence of abnormal epithelial tissue using monoclonal antibodies to the A.sub.6 B.sub.4 cell surface protein
INVENTOR(S): Quaranta, Vito, 8861 Nottingham Pl., La Jolla, CA, United States 92037
Kajiji, Shama, 104 Mistuxet Ave., Mystic, CT, United States 06355

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5320942		19940614	
APPLICATION INFO.:	US 1990-591105		19901001 (7)	<--

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1989-293384, filed on 4 Jan 1989, now abandoned which is a continuation-in-part of Ser. No. US 1987-16552, filed on 19 Feb 1987, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chan, Y. Christina
ASSISTANT EXAMINER: Budens, Robert D.
LEGAL REPRESENTATIVE: Bingham, Douglas A., Fitting, Thomas, Logan, April C.
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 31 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 1806
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1990-591105 19901001 (7) <--
DETD TABLE 4

REACTIVITY OF MONOCLONAL **ANTIBODIES** WITH FRESH FROZEN NORMAL HUMAN TISSUE SECTIONS BY IMMUNOPEROXIDASE STAINING

	HB 9318	HB 9319
Esophagus		
stratified **squamous** epithelium		
upper layers	--	3+
basal layers	4+	4+
basement membrane	4+	--
Stomach		
gastric pits	--	3+
gastric glands		
parietal cells	--	2+
chief cells	--	2+
lamina. . .	-- --	-- -- --
distal tubules	-- -- --	-- -- --
Kidney (fetal)		
glomeruli	--	3+
proximal tubules	1+	3+
distal tubules	--	3+
Cervix		
columnar epithelium		
	-- 1+	4+ 3+
basement membrane	4+ 4+	-- --
squamous epithelium		

upper layers	--	--	3+	3+
basal layers	4+	4+	4+	4+
basement membrane	4+	4+	--	--
Uterus				
endometrium	1+	--	3+	2+
myometrium. . .				

L27 ANSWER 2 OF 7 USPATFULL

ACCESSION NUMBER:	1999:18726 USPATFULL	
TITLE:	5T4 antigen from human trophoblasts	
INVENTOR(S):	Stern, Peter, Liverpool, England Hole, Nicholas, Liverpool, England	
PATENT ASSIGNEE(S):	Cancer Research Campaign Technology, Ltd., London, United Kingdom (non-U.S. corporation)	

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 5869053		19990209		
APPLICATION INFO.:	US 1993-108144		19930817	(8)	<--
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1990-571622, filed on 2 Nov 1990, now abandoned				

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1988-5240	19880504
	GB 1988-21078	19880908

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Smith, Lynette F.
LEGAL REPRESENTATIVE:	Morrison & Foerster, LLP
NUMBER OF CLAIMS:	13
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	1466
AI US 1993-108144	19930817 (8) <--
DETD	TABLE VI

L27 ANSWER 4 OF 7 USPATFULL
ACCESSION NUMBER: 94:77805 USPATFULL
TITLE: Integrin from human epithelial cells
INVENTOR(S): Quaranta, Vito, La Jolla, CA, United States
Kajiji, Shama, Mystic, CT, United States
PATENT ASSIGNEE(S): The Scripps Research Institute, La Jolla, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5344919		19940906	
APPLICATION INFO.:	US 1993-14090		19930204 (8)	<--

RELATED APPLN. INFO.: Continuation of Ser. No. US 1989-293384, filed on 4 Jan
1989, now abandoned which is a continuation-in-part of Ser. No. US 1987-16552, filed on 19 Feb 1987, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Baker, Keith
LEGAL REPRESENTATIVE: Fitting, Thomas
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1115
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1993-14090 19930204 (8) <--
DETD TABLE 4

ACCESSION NUMBER: 275705 EUROPATFULL EW 198830 FS OS STA B
TITLE: Monoclonal antibodies specific for human basal cells, SCC and precancerous cells.
Monoklonale Antikoerper, speizifisch fuer Basalzellen, SCC und Pre-Krebsartige Zellen.
Anticorps monoclonaux specifiques de cellules basales humaines, SCC et de cellules precancereuses.

INVENTOR(S): Liu, Y. S. Victor, 490 Mill Stream Drive, San Leandro California 94578, US;
Yonkovich, Shirlee J., 165 East O'Keefe, Menlo Park California 94025, US;
White, Carmen F., 11 Mirabel Avenue, San Francisco California 94110, US;
Gottfried, Toby D., 10 Rustic Way, Ordina California 94563, US;
Ranken, Raymond R., 1051 Beach Park Boulevard, No. 302, Foster City California 94404, US
PATENT ASSIGNEE(S): InTek Diagnostics, 1450 Rollins Road, Burlingame California 94010, US
PATENT ASSIGNEE NO: 931500
AGENT: Bizley, Richard Edward, et al, BOULT, WADE & TENNANT 27 Furnival Street, London EC4A 1PQ, GB

OTHER SOURCE: ESP1988026 EP 0275705 A2 880727
SOURCE: Wila-EPZ-1988-H30-T1
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES: R AT; R BE; R CH; R DE; R ES; R FR; R GB; R GR; R IT; R LI; R LU; R NL; R SE
PATENT INFO.PUB.TYPE: EPA2 EUROPAEISCHE PATENTANMELDUNG
PATENT INFORMATION:

PATENT NO	KIND	DATE
EP 275705	A2	19880727

'OFFENLEGUNGS' DATE: 19880727
APPLICATION INFO.: **EP 1987-311402** **19871223**
PRIORITY APPLN. INFO.: US 1986-946237 19861223
AI **EP 1987-311402** **19871223**
DETDEN PKK1 and PKK2

Publications:
Holfhofer, et al., Lab. Invest. 49, 317, 1983 and product inserts of **antibodies** PKK1 and PKK2 from Labsystems, Inc. Chicago, IL.

Class or Subclass of **Antibodies**:
IgG

Immunization Protocol:
Immunized with cyto.shy. skeletal proteins iso.shy. lated from pig kidney epithelial cell line.

Screening Protocol:
Primary screening used ELISA on proteins and cell lines.

Performance of **Antibodies**:

1) In human normal **squamous** epithelial tissues,

antibody PKK1 binds to cells in all layers of the strati.shy. fied system, while **antibody** PKK2 binds to the cells in basal layer and para-basal layers in normal stratified **squamous** epithelial tissues.

2) **Antibody** PKK2 binds to **columnar** epithelial tissue in normal lung.

3) **Antibody** PKK2 binds to SCC.

4) **Antibody** PKK2 binds to bronchial alveolar carcinoma.

5) No information on atypical, abnormal **squamous** epithelial tissue information.

6) PKK1 and PKK2 binds to cytokeratins.

Comments re Utility:
Distinguished tumor of epithelial. . .